(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
1 July 2004 (01.07.2004)

PCT

(10) International Publication Number
WO 2004/054518 A1

(51) International Patent Classification[7]: A61K 6/00, 9/00

(21) International Application Number:
PCT/CA2003/001943

(22) International Filing Date:
16 December 2003 (16.12.2003)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
60/433,933 16 December 2002 (16.12.2002) US

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(81) Designated States *(national)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.

(84) Designated States *(regional)*: ARIPO patent (BW, GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:
— *with international search report*
— *before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

WO 2004/054518 A1

(54) Title: TEMPORARY, PHARMACOLOGICALLY-INACTIVE DENTAL COATING FOR THE *IN SITU* PROTECTION OF DENTAL THERAPEUTIC AGENTS FROM SALIVA AND ABRASION FROM CHEWING

(57) Abstract: Topical application of a pharmacologically-inactive, inert polymeric solution to teeth affords a temporary, protective barrier for pharmacologically-active compounds that have been previously applied topically to the tooth surfaces for caries reduction. In a method of use, an aqueous dispersion polymethylmethacrylate (PMMA) and a suitable plasticizer are applied topically to the tooth surface immediately after the topical application of chlorhexidine or fluoride. The inert coating thus formed is distinct from any pharmacologically-active substance, and remains on the tooth surface until abraded by the chewing of hard foods. In a composition of matter, the solution contains ammonio methacrylate copolymer, type B USP/NF of between 20% and 35% w/w; triethyl citrate USP/NF of between 1% and 10% w/w; and purified water of between 60% and 70% w/w. The ammonio methacrylate copolymer is preferably EUDRAGIT RS 30 D brand available form Rohm GmbH.

Temporary, Pharmacologically-inactive Dental Coating for the *in situ* Protection of Dental Therapeutic Agents from Saliva and Abrasion from Chewing

Relationship to Other Applications

This application claims the benefit of United States Provisional Patent Application Number 60/433,933 filed December 16, 2002.

Background of the Invention

Field of the Invention

The invention relates to a composition of a pharmacologically-inactive coating that acts as a temporary mechanical barrier to protect an underlying layer containing pharmacologically-active agents, such as dental therapeutic agents, residing on a tooth surface, against erosion from salivary washings and abrasion from eating foods, and methods of use thereof.

Description of the Related Art

Dental caries is a chronic, asymptomatic, transmittable bacterial infection on the surface of the teeth, which affects about 20% of the population. It is the most prevalent chronic disease in adults affecting about one in three adults over the age of 50, and is also the most common pediatric disease. The dental research literature and common dental practice support the use of two common dental therapeutic compounds to combat dental caries, namely: the antimicrobial compound chlorhexidine, and the remineralizing compound fluoride. Both compounds may be administered separately in varnish modalities of varying concentrations by the dental professional to the teeth of patients in the dental office. Varnishes containing these therapeutic agents have the benefit of delivering the agent to the site of caries at relatively high concentrations compared to oral rinses or gels, of delivering these agents for reportedly long periods of time in the oral cavity, and ensuring patient compliance.

In Europe and Canada where they are approved for dental use by regulatory bodies, chlorhexidine varnishes are an accepted standard of preventive dental care.

Commercially available chlorhexidine-containing varnishes include those sold under the trademarks PREVORA (10% (w/v) chlorhexidine) by CHX Technologies, Inc., Toronto, Canada; EC40 (up to 40% (w/w) chlorhexidine) by Certichem, Nijmegen, Netherlands; and CERVITEC (1% wt chlorhexidine) by Ivoclar Vivadent, Liechtenstein.

It is reported in the scientific literature that the varnish modality is able to deliver chlorhexidine *in vitro* for between 24 hours and 3 months. See, for example,

The use of EUDRAGIT brand, or other PMMA-type polymers, to deliver drugs in the oral cavity, has been described in the patent literature as follows:

U.S. Patent No. 5,160,737 issued November 3, 1992, titled "Liquid Polymer Composition, and Method of Use" describes a liquid methacrylic acid copolymer, including EUDRAGIT acrylics, containing a releasing agent and a pharmacological agent for sustained drug release in the oral cavity.

U.S. Patent No. 5,330.746 issued July 19, 1994 titled "Dental Varnish Composition and Method of Use" describes an oral composition for plaque prevention and tooth hypersensitivity consisting of an antibacterial agent embedded in a carrier such as an acrylic polymer, and preferably an EUDRAGIT acrylic, and the use of this composition to prevent caries.

U.S. Patent No. 6,197,331, March 6, 2001, titled "Pharmaceutical Oral Patch for Controlled Release of Pharmaceutical Agents in the Oral Cavity" describes a EUDRAGIT-based device containing active pharmaceutical compounds in a polymer matrix which is not bonded to the teeth and which can be removed from the mouth.

U.S. Patent Application No. 20010024657 published September 27, 2001 titled "Pharmaceutical Oral Patch for Controlled Release of Pharmaceutical Agents in the Oral Cavity," which is a continuation-in-part to U.S. Patent No. 6,197,331, describes a singular oral composition possibly containing PMMA, including EUDRAGIT polymers, and a pharmaceutically active component for application to the teeth.

References in the scientific literature to methacrylic coatings for drug release purposes in the oral cavity include the following:

Diarra, *et al.* describe a 200 mg tablet consisting of a granular matrix of hydroxyapatite, ethyl cellulose and EUDRAGIT polymers, along with an active drug substance, which is then fixed on to the tooth for sustained release of the pharmacologically active substance; see, M. Diarra, *et al.*, "Elaboration and Evaluation of an Intraoral Controlled Release Delivery System," *Biomaterials*, Vol. 19, pp. 1523-1527 (1998).

Patel, *et al.* describe a rigid polymeric device consisting of polyethyl methacrylate and tetrahydrofurfuryl plus chlorhexidine for the reduction of fungus in the oral cavity; the device was tested *in vitro* for its reduction of *Candida albicans*. See M. Patel, *et al.*, "A polymeric system for the intra-oral delivery of an anti-fungal agent," *Biomaterials*, Vol. 22, pp. 2319-2324 (2001).

The aforementioned patents and scientific publications incorporating PMMA-type polymers in the oral cavity are directed to one-stage drug delivery formulations,

compound chlorhexidine, and the remineralizing compound fluoride, both of which are known to be effective in the treatment and prevention of dental caries.

Clorhexidine, for example, has a bitter taste, and the provision of an inert mechanical barrier layer helps to improve the acceptance of these therapeutic agents by the patient and, hence, the patient's compliance to treatment. Thus, higher concentrations of therapeutic agents can be administered to the patient over a longer period of time.

Because the formulation is intended for as an oral composition, it should have acceptable taste, clarity, color, durability and application characteristics for the dental professional, as well as biocompatibility to permit its use on patients' teeth as a separate temporary protective coating for dental therapeutic compounds.

In a preferred embodiment of this aspect of the invention, an aqueous dispersion of a polymethylmethacrylate copolymer includes a sufficient amount of a plasticizer to form a film *in situ* when applied to a tooth surface that has appropriate flexibility and that dries quickly in the oral cavity. Polymethylmethacrylate copolymers, suitable for the practice of the invention, are commercially available, such as the copolymers of methacrylic acid and methacrylate marketed by Rohm GmbH, Darmstadt, Germany as the EUDRAGIT brand family of polymethylmethacrylates.

In a particularly preferred embodiment of the invention, the polymethylmethacrylate is an ammonio methacrylate copolymer type B USP/NF, such as EUDRAGIT RS 30 D brand polymethylmethacrylate. EUDRAGIT RS 30 D conforms to the specifications of an ammonio methacrylate copolymer, Type B in the U.S. Pharmacopeia and the U.S. National Formulary. EUDRAGIT RS 30D, which is an aqueous dispersion of acrylic polymer, has been used according to the manufacturer's directions of use and industry standards, as an approved pharmaceutical and cosmetic excipient in oral and dermal applications for drug delivery in solid dosage forms in the gastrointestinal tract or on the skin for many years.

Suitable plasticizers for the PMMA include pharmaceutical grade triethyl citrate, dibutyl sebacate, dibutyl phthalate, and diethyl phthalate, and the like. Triethyl citrate, however, is particularly preferred. Preferred concentrations of plasticizer range from between 1% w/w and 20% w/w. In the formulation process, the plasticizer is preferably added to the aqueous dispersion of PMMA over a period of between 10 and 30 minutes.

In a further method aspect of the invention, a method of preventing or reducing the incidence of caries in teeth, includes the steps of applying a liquid coating of pharmacologically-active substances of the type used to reduce caries to a tooth surface; followed by applying a pharmacologically inert barrier coating, in accordance with the present invention, on top of the coating containing the pharmacologically-active substance. The inert barrier coating serves as a temporary mechanical barrier to delay erosion of the therapeutic coating caused by the washings of saliva and abrasion caused by eating food. Preferably, the coatings are dried by the dental professional.

Of course, the components used in the practice of the method aspect of the invention can be provided as a two component kit, the ingredients of which are capable of reducing caries in the oral cavity. This embodiment would provide a separate compositions, the first composition including a therapeutic agent, such as chlorhexidine and/or fluoride and the second composition in accordance with the present invention comprising, for example, a PMMA in an aqueous dispersion with sufficient triethyl citrate to ensure flexibility and rapid drying in the oral cavity.

DETAILED DESCRIPTION OF THE INVENTION

In accordance with a specific illustrative embodiment of the invention, a pharmacologically inert, bio-acceptable, liquid formulation of a water-suspended PMMA and plasticizer is formulated as follows:

28% EUDRAGIT RS 30 D polymethylmethacrylate;

6% triethyl citrate; and

66% w/w water.

A dental professional applies this formulation to the surface of teeth in a dental patient with a brush following the application of a coating of a pharmacologically-active substance, specifically chlorhexidine and/or fluoride in accordance with methods that are known and practiced in the art. Preferably, the first coating is dried, such as with an air syringe, or is permitted to dry prior to application of the pharmacologically-inert barrier coating.

In the clinical results reported herein, the pharmacologically-active layer was a chlorhexidine (10% w/v) solution sold under the trademark PREVORA by CHX Technologies, Inc., Toronto, Canada.

Although the invention has been described in terms of specific embodiments and applications, persons skilled in the art may, in light of this teaching, generate additional embodiments without exceeding the scope or departing from the spirit of the claimed invention. Accordingly, it is to be understood that the drawing and description in this disclosure are proffered to facilitate comprehension of the invention and should not be construed to limit the scope thereof.

12. A method for protecting pharmacologically-active substances applied in a temporary coating to a surface of a tooth comprising:

applying a pharmacologically inert barrier coating of a polymethylmethacrylate and a plasticizer on top of the temporary coating containing the pharmacologically-active substance to serve as a temporary mechanical barrier against the washings of saliva and abrasion caused by eating food.

13. The method of claim 12 wherein the pharmacologically-active substance(s) comprise one or more active agents of the type known to reduce caries when applied to the tooth.

14. The method of claim 13 wherein the pharmacologically-active substances are selected from the group consisting of chlorhexidine and fluoride.

15. The method of claim 12 wherein the polymethylmethacrylate is water-dispersed and the plasticizer is a pharmaceutical grade plasticizer selected from the group consisting of triethyl citrate, dibutyl sebacate, dibutyl phthalate, and diethyl phthalate.

16. The method of claim 12 wherein the polymethylmethacrylate is an ammonio methacrylate copolymer, type B USP/NF.

17. The method of claim 16 wherein the ammonio methacrylate copolymer is EUDRAGIT RS 30 D brand polymethylmethacrylate.

18. A method of preventing or reducing the incidence of caries in teeth, comprising the steps of:

a. applying a liquid coating of pharmacologically-active substances of the type used to reduce caries to a tooth surface; and

b. applying a pharmacologically inert barrier coating of a polymethylmethacrylate and a plasticizer on top of the coating containing the pharmacologically-active substance to serve as a temporary mechanical barrier against the washings of saliva and the abrasion from eating foods.